↓

William Hayes: Pioneering Contributions Remembered

After Hayes proposed oriented partial chromosome transfer during bacterial conjugation, microbial genetics took a great leap forward

SIMON SILVER, JAMES SHAPIRO, NEIL MENDELSON, PAUL BRODA, AND JON BECKWITH

William Hayes, who died in January 1994 in Australia, made a series of striking discoveries in microbial genetics 40 years ago. While serving as a senior lecturer at the Royal Postgraduate Medical School at Hammersmith Hospital in London during the early 1950s, his insights describing the nature of bacterial conjugation and gene transfer set the stage for major advances in bacterial genetics and, more broadly, molecular biology in the decades that followed. In a remarkably productive 2 years, Hayes outlined how bacterial conjugation involves ordered transfer of chromosome segments from a donor ("male") cell to a recipient ("female") cell rather than by cell fusion, identified the nonchromosomal F factor in *Escherichia coli* that determines maleness in such bacterial cells, and isolated a male donor strain with 10 thousand times the ordinary gene transfer frequency. In addition to his research on conjugation and sex plasmids, Hayes established the first microbial genetics research unit and wrote the defining textbook on microbial molecular genetics.

Hayes was educated and had his first exposure to medical research in Ireland before World War II. During the war, he served as a medical officer with the British in India, where he also began conducting bacterial research.

After the war, Hayes returned to Dublin with an appointment in bacteriology at Trinity College, but he soon moved to London to become a senior lecturer at the Royal Postgraduate Medical School. There, motivated by a desire to apply genetic analysis to the phase variation problem, he began work in earnest on bacterial genetics. During the year of his move to London, Hayes met Luigi L. Cavalli-Sforza at a summer course in bacterial chemistry in Cambridge. The meeting proved crucial, as it was Cavalli who provided Hayes with the *E. coli* K-12 strains with which he conducted his pivotal studies in bacterial genetics.

In striking contrast to the high technology of current molecular genetics, Hayes' best work was done with very limited technical facilities. For example, incubators in India were cooled by fans, and calibrated wire loops rather than glass pipettes were used in analyzing conjugation kinetics in London. Despite (or perhaps because of) limited facilities, elegant thinking more than made up for lack of equipment, and Hayes' experiments were to prove of fundamental importance.

Hayes' 1952 Model for Conjugation Was an Intellectual Bombshell

Although bacterial conjugation was recognized as early as 1946, the investigators studying it had difficulty understanding the mechanism. When Hayes presented a clear, straightforward, and ultimately correct model for bacterial conjugation at a small meeting in Pallanza, Italy, in September 1952, it seemed that "a

Simon Silver (corresponding author) is at the Department of Microbiology and Immunology, University of Illinois, Chicago; James Shapiro is at the Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, Ill.; Neil Mendelson is at the Department of Molecular and Cell Biology, University of Arizona, Tucson; Paul Broda is at the Department of Biochemistry, University of Manchester Institute of Science and Technology, Manchester, United Kingdom; and Jon Beckwith is at the Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, Mass. All were associated with William Hayes in the 1960s.

bombshell had exploded," as James Watson later wrote. In his deceptively modest way, Hayes abruptly overturned layers of speculative explanations that members of the microbial genetics community had put forward in an effort to make sense of a set of then-confusing observations.

Until that meeting in Italy, most microbial geneticists took little note of Hayes' results, although he had proposed his model of unidirectional gene transfer that April at a meeting in Oxford and published his experimental results and model a few months earlier in January 1952. Instead, the attention of that research community had focused on the explanations for conjugation championed by Joshua Lederberg, who was then at the University of Wisconsin. Lederberg, who had discovered bacterial conjugation some 6 years earlier, explained the phenomenon in terms of the fusion of two bacterial cells.

According to Lederberg's model, this process of cell fusion was followed by a complex series of steps involving the segregation and selective loss of genetic markers from the two complete sets of chromosomes that were initially present in the fusion cell.

Hayes' results and his model were no secret when they were presented in Italy. Nonetheless, they proved a bombshell to the consciousness of the scientific community. Lederberg did not immediately accept the simplifying model. Instead, he continued to explore his radically different model of cell fusion. Nevertheless, the data were wonderfully reproducible in, and exchanged freely between, both laboratories.

The Hayes Model Produced Immediate Ripples

Hayes' Pallanza bombshell provided a simple and elegant—if highly unorthodox in the history of genetics—basis for explaining the available results. He soon attracted several important collaborators.

For example, Elie L. Wollman of the Institut Pasteur in Paris, France, who had heard of Hayes' findings, visited him in London, where they agreed to do joint experiments on the kinetics of conjugation. Wollman and François Jacob, who was also at the Institut Pasteur, conducted detailed studies of chromosomal linkage based on the kinetics of gene transfer from donor to recipient cells during conjugation. Within a few years, these findings led to the correct understanding of the linear order of *E. coli* genes on a single circular chromosome.

Watson began visiting Hayes in London after the Pallanza meeting, and they soon published an analysis of genetic linkage relationships in *E. coli*. Hayes was invited to the 1953 symposium held in Cold Spring Harbor, New York, where Watson announced the double-helical structure of DNA.

At that symposium, Hayes described the discovery of the second high-frequency (Hfr) donor *E. coli* strain and its use in unraveling the mysteries of the conjugation process. The two first independently discovered Hfr strains are still called Hfr Cavalli and Hfr Hayes. Hayes' presentation helped set the stage for use of *E. coli* as the standard organism for investigating microbial genetics and molecular biology.

During the 1953 visit to the United States, Hayes continued to study the kinetics of bacterial conjugation during a 6-month sabbatical leave with Max Delbrück at the California Institute of Technology (CalTech) in Pasadena, Calif. The friendship with Delbrück continued, leading to a postretirement sabbatical year that Hayes spent at CalTech some 25 years later.

Hayes' Early Achievements in Perspective

During 1950–1953 Hayes made three extraordinary discoveries and realizations: (i) he demonstrated that bacterial conjugation involves the unidirectional transfer of genes from a donor to a recipient cell rather than something equivalent to cell fusion (as between egg and sperm) or reciprocal exchange of nuclei (as in *Paramecium* spp.); (ii) he discovered the fertility factor F, the first recognized nonchromosomal bacterial plasmid, and showed that it is present in donor cells but absent in recipient cells; and (iii) he helped to outline the process of high-frequency, ordered gene transfer from the Hfr donor, studies of which led eventually to the single genetic map and a rational explanation of earlier recombinational mapping data.

These efforts radically changed then-current thinking on bacterial conjugation from baroque to simple. Hayes' contributions seemed at first counter-intuitive but proved correct as well as elegant. In appreciating the general agonizing that often accompanies such turnabouts, Hayes referred to a favorite passage from the Hilaire Belloc poem, "The Microbe." It ends with the following ironic lines: "But scientists, who ought to know, assure us that they must be so... Oh! let us never, never doubt what nobody is sure about!"

According to Hayes, "There (was) little doubt as to the validity of the results themselves. Their interpretation, however, [was] controversial." His first bacterial genetics paper in 1952 established the inequality of the two partner cells in conjugation. He found that only one of the partners needs to be alive; the other could be killed (even hours earlier) by streptomycin and still participate! From those results, he concluded intuitively that one cell acted as donor (and need not be viable) and the other as recipient in a process of one-way transfer of genetic material. Years passed before there was a compelling proof of this hypothesis by micromanipulation experiments, which analyzed the properties of single exconjugant cells.

Hayes and, independently, Lederberg and colleagues found that bacterial "fertility"—that is, the ability of a bacterial strain to participate in conjugation—is itself a hereditary property and is associated with a transferrable nonchromosomal factor called F. Hayes initially thought this gene transfer property could be attributed to a "gamete" similar to a phage particle, rather than to the naked DNA plasmid and actual cell-to-cell direct transfer that we now understand.

Hayes later remembered that he devised but discarded a number of other hypotheses to explain aspects of conjugation, including one calling for three separate or branched chromosomes to explain complex recombinational data. These ideas frequently proved wrong, and near the end of his career he said he was glad that he published very few papers during this early period.

Subsequent Career

In 1957, the British Medical Research Council recognized Hayes' achievements by establishing a Microbial Genetics Research Unit at Hammersmith Hospital, where he gathered a group of younger investigators (including at different times all of us) and encouraged a broad range of experimental work.

Over the years, the British members of the staff included Roy Clowes, Willie Donachie, Ken Fisher, Stuart Glover, Elinor Meynell, Bob Pritchard, Ken Stacey, and Neville Symonds. Paul Broda, Ken Fisher, Julian Gross, Marilyn Monk, Don Ritchie, and John Scaife made up the cadre of early Ph.D. students. An extraordinary number went on to head their own research efforts elsewhere. Naomi Datta did her pioneering work on antibiotic resistance plasmids in a nearby building at Hammersmith. As unit head, Hayes was exceptional in facilitating the work of others without intruding or narrowly directing it.

William Hayes in 1992

Hayes' gift for working with junior scientists was recognized as unusual, and some colleagues have considered these mentoring efforts equal in value to his experimental achievements. Moreover, Hayes was unusually egalitarian, particularly during this postwar period in socially stratified England. Thus, Norrie Bonfil, who ran the microbiology kitchen, and Deidre Nadal, who handled the office with skill and understanding, were equal members of his Hammersmith "family."

Besides encouraging young investigators and directing a new unit, Hayes committed at least 2 solid years to writing his outstanding book, *The Genetics of Bacteria and their Viruses*, which was known affectionately as "The Bible" for a time. Many microbiologists consider this book his third major achievement. And certainly no single author has felt up to the task of writing such a comprehensive volume since.

In 1968, the Medical Research Council (MRC) Unit at Hammersmith moved from London to Edinburgh (along with another London MRC group). There, Hayes and Martin Pollock formed the first department of molecular biology in a British university. With a core group from their London laboratories and a number of equally gifted new staff members, the Edinburgh laboratory proved a second great leadership success towards the end of the mainly administrative phase of Hayes' career.

With the Edinburgh effort running effectively, Hayes moved 6 years later to occupy the chair of genetics at the Australian National University in Canberra. Although he hoped to be relieved of administrative duties by this move and to get "back to the bench," the conditions in Canberra did not permit him to realize that wish. Hayes retired in 1978, and after a stay at CalTech (again with Max Delbrück), he ended his career as a visiting fellow at the Australian National University, working with his protege Peter Gresshoff, who subsequently moved to the University of Tennessee.

In retirement, Hayes remained in Australia, moving in 1986 to north of Sydney. During these final years, Bill grew increasingly frustrated by progressive Alzheimer's disease. He died peacefully on 7 January 1994, of coronary failure.

Bill Hayes' version of the discovery of F and the nature of bacterial conjugation is presented in the 1966 Festschrift to Max Delbrück. From what we know of his modest and direct way of expressing himself, this account can be taken as fair and accurate. A detailed description of Hayes' achievements is in preparation for a memoir for the Royal Society of Britain. ◻

Suggested Reading

Brock, T. D. 1990. Section 5.4. The pre-Hayes era of bacterial genetics, p. 87–88, and Section 5.5. The work of William Hayes, p. 88–90. *In* Emergence of bacterial genetics. Cold Spring Harbor Press, Cold Spring Harbor, N.Y.

Coakley, D. 1992. William Hayes b 1913. p. 345–357. *In* Irish masters of medicine. Town House, Dublin.

Hayes, W. 1952. Recombination in *Bact. coli* K 12: unidirectional transfer of genetic material. Nature (London) 169:118–119.

Hayes, W. 1952. Genetic recombination in *Bact. coli* K12: analysis of the stimulating effect of ultra-violet light. Nature (London) 169: 1017–1018.

Hayes, W. 1953. Observations on a transmissible agent determining sexual differentiation in *Bacterium coli*. J. Gen. Microbiol. 8:72–88.

Hayes, W. 1953. The mechanism of genetic recombination in *Escherichia coli*. Cold Spring Harbor Symp. Quant. Biol. 18:75–93.

Hayes, W. 1964. The genetics of bacteria and their viruses. Blackwell Scientific Publishers, Oxford. (Also a 2nd ed., 1968.)

Hayes, W. 1966. Sexual differentiation in bacteria, p. 201–215. *In* J. Cairns, G. S. Stent, and J. D. Watson (ed.), Phage and the origins of molecular biology. Cold Spring Harbor Laboratory of Quantita-

tive Biology, Cold Spring Harbor, N.Y.
Judson, H. F. 1979. The eighth day of creation. Simon and Schuster, New York.
Lederberg, J., L. L. Cavalli, and E. M. Lederberg. 1952. Sex compatibility in *Escherichia coli*. Genetics 37:720–730.
Stent, G. S. 1971. Chapter 10. Conjugation, p. 251–297. *In* Molecular genetics. An introductory narrative. W. H. Freeman and Company, San Francisco.
Watson, J. D. 1968. The double helix. Atheneum, New York.
Wollman, E.-L., F. Jacob, and W. Hayes. 1956. Conjugation and genetic recombination in *Escherichia coli* K-12. Cold Spring Harbor Symp. Quant. Biol. 21:141–162.